

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
21 June 2001 (21.06.2001)

PCT

(10) International Publication Number
WO 01/44239 A3

(51) International Patent Classification⁷: C07D 413/12,
413/14, 403/14, 487/04, 261/16, 401/12, 417/12, A61K
31/42, A61P 9/12

08822 (US). GU, Zhengxiang [CN/US]; 92 York Road,
Princeton, NJ 08540 (US).

(21) International Application Number: PCT/US00/33730

(74) Agents: ALGIERI, Aldo, A. et al.; Bristol-Myers Squibb
Co., P.O. Box 4000, Lawrenceville-Princeton Road,
Princeton, NJ 08543 (US).

(22) International Filing Date:
13 December 2000 (13.12.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/464,037 15 December 1999 (15.12.1999) US
09/481,197 11 January 2000 (11.01.2000) US
09/513,779 25 February 2000 (25.02.2000) US
09/604,322 26 June 2000 (26.06.2000) US
09/643,640 22 August 2000 (22.08.2000) US

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE,
DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID,
IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT,
LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL,
PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ,
UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF,
CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

(71) Applicant (*for all designated States except US*): BRIS-
TOL-MYERS SQUIBB CO. [US/US]; P.O. Box 4000,
Lawrenceville-Princeton Road, Princeton, NJ 08543-4000
(US).

Published:
— with international search report

(72) Inventors; and
(75) Inventors/Applicants (*for US only*): MURUGESAN,
Natesan [US/US]; 42 Millbrook Drive, Princeton Junc-
tion, NJ 08550 (US). TELLEW, John, E. [US/US]; 28
Avalon Road, Pennington, NJ 08534 (US). MACOR,
John, E. [US/US]; 258 Old Farm Road, Flemington, NJ

(88) Date of publication of the international search report:
1 November 2001

*For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.*



WO 01/44239 A3

(54) Title: BIPHENYL SULFONAMIDES AS DUAL ANGIOTENSIN ENDOTHELIN RECEPTOR ANTAGONISTS

(57) Abstract: Novel biphenyl sulfonamide compounds which are combined angiotensin and endothelin receptor antagonists are claimed along with methods of using such compounds in the treatment of conditions such as hypertension and other diseases, as well as pharmaceutical compositions containing such compounds.

INTERNATIONAL SEARCH REPORT

International Application No

PC US 00/33730

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D413/12 C07D413/14 C07D403/14 C07D487/04 C07D261/16
 C07D401/12 C07D417/12 A61K31/42 A61P9/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 612 359 A (MURUGESAN) 18 March 1997 (1997-03-18) column 4, line 58 -column 6, line 2; claims; example 15 ---	1-46
X	US 5 846 990 A (MURUGESAN) 8 December 1998 (1998-12-08) claims; examples ---	26
Y	US 5 780 473 A (MURUGESAN ET. AL.) 14 July 1998 (1998-07-14) column 6, line 33 -column 7, line 45; claims; examples ---	1-46
Y	US 5 514 696 A (MURUGESAN ET. AL.) 7 May 1996 (1996-05-07) column 5, line 13 -column 6, line 2; claims; examples ---	1-46
	--- -/--	

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

15 May 2001

Date of mailing of the international search report

29.05.01

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Authorized officer

Helps, I

INTERNATIONAL SEARCH REPORT

International Application No

PC JS 00/33730

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	GB 2 264 710 A (MERCK & CO) 8 September 1993 (1993-09-08) claims; examples ---	1-46
X	WO 98 33780 A (BRISTOL MYERS SQUIBB) 6 August 1998 (1998-08-06) claims; examples ---	1,26,39
X	WO 98 04260 A (BRISTOL MYERS SQUIBB) 5 February 1998 (1998-02-05) claims; examples ---	26
Y	US 5 554 625 A (RIVERO ET. AL.) 10 September 1996 (1996-09-10) claims; examples ---	1
Y	US 5 399 578 A (BÜHLMAYER ET. AL.) 21 March 1998 (1998-03-21) claims; examples ---	1,39
Y	US 5 260 328 A (MARKWALDER ET. AL.) 9 November 1993 (1993-11-09) column 2, line 1 - line 38; claims; examples ---	1,39
Y	US 5 760 038 A (MURUGESAN ET. AL.) 2 June 1998 (1998-06-02) claims; examples -----	1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 00/35730

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 23 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1(part),2-25,27-31,32(part),33-37,39-46

Compounds of formula I in which R1 is A, B, E, G - N

2. Claims: 1(part),32(part),38

Compounds of formula I in which R1 is D

3. Claim : 1(part)

Compounds of formula I in which R1 is F

4. Claim : 1(part)

Compounds of formula I in which R1 is O

5. Claim : 26

Compounds of formula LXX.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PC US 00/33730

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5612359 A	18-03-1997	US 5827869 A	27-10-1998
		AU 699138 B	26-11-1998
		AU 3026195 A	07-03-1996
		CA 2155447 A	27-02-1996
		CN 1128262 A,B	07-08-1996
		CZ 9502163 A	13-03-1996
		EP 0702012 A	20-03-1996
		FI 954008 A	27-02-1996
		HU 74097 A	28-11-1996
		IL 114829 A	30-11-1999
		JP 8183786 A	16-07-1996
		NO 953361 A	27-02-1996
		NZ 272812 A	24-11-1997
		PL 310191 A	04-03-1996
		SG 46142 A	20-02-1998
		BR 1100659 A	13-06-2000
US 5846990 A	08-12-1998	AU 720458 B	01-06-2000
		AU 2209897 A	02-09-1997
		CA 2240043 A	21-08-1997
		EP 0921800 A	16-06-1999
		WO 9729748 A	21-08-1997
		ZA 9701423 A	19-08-1998
US 5780473 A	14-07-1998	US 5760038 A	02-06-1998
		AU 3661397 A	20-02-1998
		WO 9804260 A	05-02-1998
		AU 708926 B	19-08-1999
		AU 4331496 A	15-08-1996
		CA 2168154 A	07-08-1996
		CN 1138581 A,B	25-12-1996
		CZ 9600292 A	11-09-1996
		EP 0725067 A	07-08-1996
		FI 960516 A	07-08-1996
		HU 9600256 A	28-10-1997
		JP 8245600 A	24-09-1996
		NO 960473 A	07-08-1996
		NZ 280879 A	24-11-1997
		PL 312650 A	19-08-1996
		SG 46218 A	20-02-1998
US 5514696 A	07-05-1996	US 6107320 A	22-08-2000
		AT 149155 T	15-03-1997
		AU 3838293 A	11-11-1993
		CA 2095174 A	07-11-1993
		CN 1084515 A	30-03-1994
		CY 2016 A	20-02-1998
		DE 69308229 D	03-04-1997
		DE 69308229 T	17-07-1997
		DK 569193 T	17-03-1997
		EP 0569193 A	10-11-1993
		ES 2100459 T	16-06-1997
		FI 932052 A	07-11-1993
		GR 3023421 T	29-08-1997
		HK 98197 A	08-08-1997
		HU 65751 A,B	28-07-1994
		IL 105481 A	05-12-1996
		JP 6049046 A	22-02-1994

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PC JS 00/33730

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5514696 A		MX 9302618 A	31-05-1994
		NO 303065 B	25-05-1998
		NZ 247440 A	27-04-1995
		PL 298828 A	27-12-1993
		RU 2133742 C	27-07-1999
		ZA 9302914 A	12-11-1993

GB 2264710 A	08-09-1993	NONE	

WO 9833780 A	06-08-1998	AU 730111 B	22-02-2001
		AU 6134998 A	25-08-1998
		BR 9807098 A	18-04-2000
		CN 1244862 T	16-02-2000
		CZ 9902362 A	17-11-1999
		EP 0996618 A	03-05-2000
		NO 993691 A	29-07-1999
		PL 334773 A	13-03-2000
		US 6043265 A	28-03-2000

WO 9804260 A	05-02-1998	US 5780473 A	14-07-1998
		AU 3661397 A	20-02-1998

US 5554625 A	10-09-1996	AU 4770893 A	14-02-1994
		EP 0668864 A	30-08-1995
		JP 7509464 T	19-10-1995
		WO 9402142 A	03-02-1994

US 5399578 A	21-03-1995	US 5965592 A	12-10-1999
		AT 134624 T	15-03-1996
		AU 644844 B	23-12-1993
		AU 7115191 A	22-08-1991
		CA 2036427 A	20-08-1991
		CA 2232775 A	20-08-1991
		CY 1978 A	05-09-1997
		DE 59107440 D	04-04-1996
		DK 443983 T	18-03-1996
		EP 0443983 A	28-08-1991
		ES 2084801 T	16-05-1996
		FI 910747 A	20-08-1991
		FI 980787 A	06-04-1998
		GR 3019155 T	31-05-1996
		HK 219996 A	03-01-1997
		HU 61271 A	28-12-1992
		IE 910548 A	28-08-1991
		IL 97219 A	08-12-1995
		JP 2749458 B	13-05-1998
		JP 4235149 A	24-08-1992
		KR 171409 B	01-02-1999
		LU 90100 A	25-09-1997
		LU 90362 A	10-05-1999
		LV 5773 A	20-12-1996
		MX 24598 A	28-02-1994
		NO 304023 B	12-10-1998
		NZ 237126 A	25-11-1994
		PT 96799 A,B	31-10-1991
		ZA 9101179 A	27-11-1991

US 5260328 A	09-11-1993	US 5352676 A	04-10-1994

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

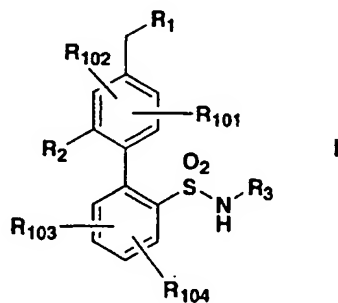
PCT/US 00/33730

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5260328 A		AT 99934 T	15-01-1994
		AU 5416990 A	05-11-1990
		CA 2030530 A	07-10-1990
		DD 298478 A	27-02-1992
		DE 69005974 D	24-02-1994
		DE 69005974 T	05-05-1994
		WO 9011760 A	18-10-1990
		EP 0423269 A	24-04-1991
		HU 58518 A	30-03-1992
		JP 3505332 T	21-11-1991
		PT 93680 A	20-11-1990
		US 5196445 A	23-03-1993
		ZA 9002649 A	30-01-1991
US 5760038 A	02-06-1998	AU 708926 B	19-08-1999
		AU 4331496 A	15-08-1996
		CA 2168154 A	07-08-1996
		CN 1138581 A,B	25-12-1996
		CZ 9600292 A	11-09-1996
		EP 0725067 A	07-08-1996
		FI 960516 A	07-08-1996
		HU 9600256 A	28-10-1997
		JP 8245600 A	24-09-1996
		NO 960473 A	07-08-1996
		NZ 280879 A	24-11-1997
		PL 312650 A	19-08-1996
		SG 46218 A	20-02-1998
		US 5780473 A	14-07-1998

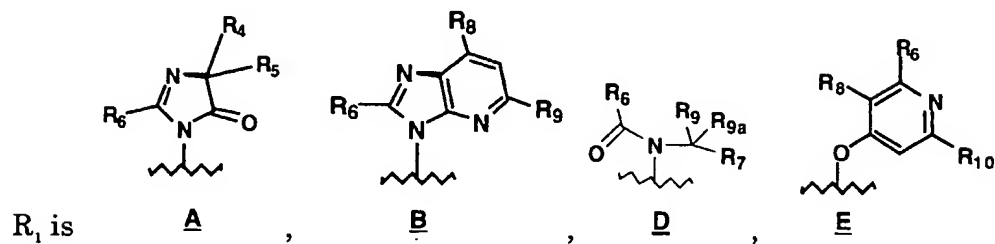
What is claimed is:

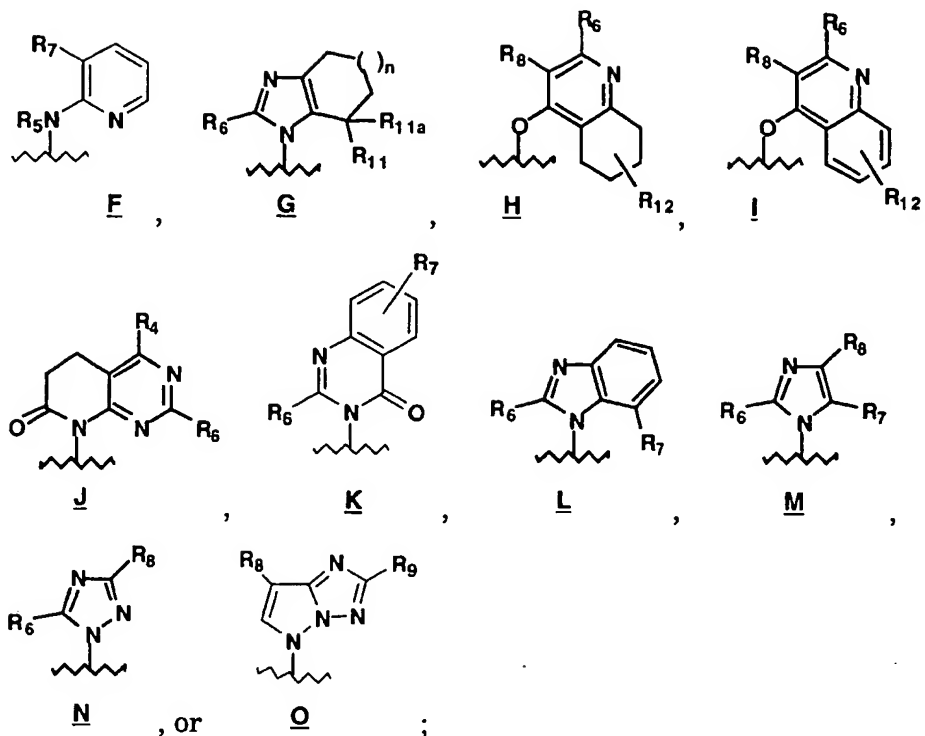
1. A compound of the following formula I, or an enantiomer, diastereomer, salt or metabolite thereof:

5



wherein:





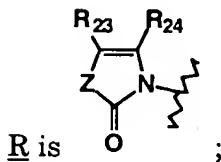
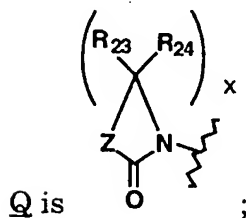
R_2 is hydrogen, halogen, -CHO, alkyl, haloalkyl, (cycloalkyl)alkyl, alkenyl,
 5 alkylnyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, aryloxy alkoxyalkoxy,
 cyano, hydroxy, hydroxyalkyl, nitro, $-\text{CH}(\text{OR}_{13})(\text{OR}_{14})$, $-(\text{CH}_2)_w\text{Y}$;
 with the proviso that when R_1 is B, R_2 is not hydrogen, halogen,
 alkyl, haloalkyl, alkoxy, hydroxyalkyl, nitro, $-(\text{CH}_2)_w\text{NR}_{19}\text{R}_{20}$ or
 $-\text{NHSO}_2\text{R}_{22}$;

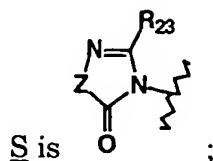
10 R_3 is heteroaryl;

R_4 and R_5 are each independently alkyl, hydroxyalkyl, cycloalkyl, hydroxy
 substituted cycloalkyl, alkoxyalkyl, or hydroxy substituted
 alkoxyalkyl, or R_4 and R_5 together form a cyclobutyl, cyclopentyl,
 cyclohexyl, tetrahydrofuranyl or tetrahydropyranyl ring which may
 15 be optionally substituted with one or more hydroxy groups;

R_6 is alkyl, hydroxyalkyl, haloalkyl, hydroxy substituted haloalkyl,
 cycloalkyl, hydroxy substituted cycloalkyl, (cycloalkyl)alkyl,
 hydroxy substituted (cycloalkyl)(alkyl), aralkyl, alkoxy, hydroxy
 substituted alkoxy, alkoxyalkyl, hydroxy substituted alkoxyalkyl, or
 20 $-\text{NR}_{16}\text{R}_{17}$;

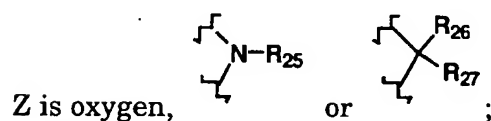
- R_7 is $-(CH_2)_w-CO_2R_{15}$, $-(CH_2)_w-(C=O)NR_{16}R_{17}$, $-(CH_2)_w-NR_{15}(C=O)NR_{16}R_{17}$, $-(CH_2)_w-CH_2OH$, $-(CH_2)_w-(C=O)R_{15}$, tetrazolyl, oxadiazolyl or triazolyl wherein said tetrazolyl, oxadiazolyl or triazolyl may optionally be substituted with hydrogen, alkyl, hydroxy or halogen;
- 5 R_8 , R_9 , R_{9a} , R_{10} and R_{12} are each independently hydrogen, halogen, alkyl, hydroxyalkyl, cycloalkyl, (cycloalkyl)alkyl, aryl, heteroaryl, arylalkyl, alkylthioalkyl, alkoxy or alkoxyalkyl, or R_9 and R_{9a} together with the carbon atom to which they are bonded form a cycloalkyl ring;
- 10 R_{11} and R_{11a} are each independently hydrogen, alkoxy, or together form a carbonyl;
- R_{13} and R_{14} are alkyl or together form a five to six-membered ring;
- R_{15} , R_{16} and R_{17} are independently hydrogen, alkyl, hydroxyalkyl, cycloalkyl, (cycloalkyl)alkyl, alkoxyalkyl, aralkyl, heterocycloalkyl,
- 15 aryl, heteroaryl or $-(CH_2)_wQ$, or R_{16} and R_{17} may together form a four to six-membered heterocyclic ring;
- n is 1 or 2;
- w is 0, 1, or 2;
- Y is heteroaryl, $-COOH$, $-COOR_{18}$, $-CONR_{19}R_{20}$, $-NR_{19}R_{20}$, $-NR_{19}-OR_{20}$,
- 20 $-NR_{21}(C=O)R_{22}$, $-NR_{21}(C=O)NR_{19}R_{20}$, $-N(R_{19})-(alk)-NR_{21}(C=O)R_{22}$, $-NR_{21}(C=O)OR_{18}$, $-NR_{21}SO_2R_{22}$, $-SO_2R_{22}$, Q , R or S ;





R_{18} , R_{19} , R_{20} , R_{21} and R_{22} are each independently hydrogen, alkyl, haloalkyl, alkoxyalkyl, cycloalkyl, alkenyl, alkynyl, aryl, aralkyl, heteroaryl, or R_{19} and R_{20} may together form a four to seven-membered heterocyclic ring;

R_{23} and R_{24} are each independently hydrogen, alkyl or cycloalkyl, or may together form a three to seven membered cycloalkyl ring;

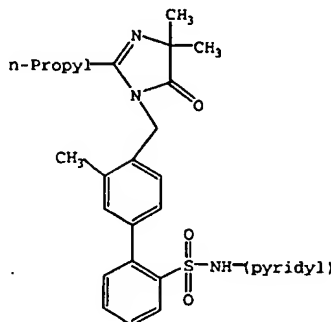


x is 2, 3 or 4;

R_{25} , R_{26} and R_{27} are each independently hydrogen, alkyl or cycloalkyl, or R_{26} and R_{27} may together form a three to seven-membered cycloalkyl ring;

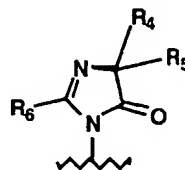
R_{101} , R_{102} , R_{103} , and R_{104} are each independently hydrogen, halogen, -CHO, alkyl, haloalkyl, (cycloalkyl)alkyl, alkenyl, alkynyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, alkoxyalkoxy, cyano, hydroxy, hydroxyalkyl, nitro, -CH(OR₁₃)(OR₁₄), or -(CH₂)_wY; wherein said rings; aryl alone or as part of another group; or heteroaryl alone or as part of another group may each optionally be substituted by one or more hydrogen, halogen, cyano, alkyl, hydroxyalkyl, alkoxy, nitro or trifluoromethyl groups;

provided that when R_1 is A said compound is other than



2. A compound of claim 1, wherein R_3 is isoxazol-5-yl or isoxazol-3-yl independently substituted with two substituents independently selected from alkyl or halogen.

5



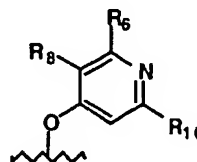
3. A compound of claim 2, wherein R_1 is

A

4. A compound of claim 3, wherein R_2 is alkyl, haloalkyl, alkoxyalkyl or haloalkoxyalkyl and R_{101} , R_{102} , R_{103} , R_{104} are each
10 independently hydrogen, halogen, or alkyl.

5. A compound of claim 3, wherein R_2 is $-CH_2Y$.

6. A compound of claim 5, wherein Y is Q.



15

7. A compound of claim 2, wherein R_1 is

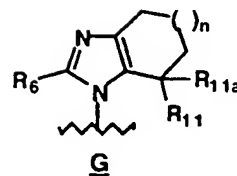
E

8. A compound of claim 7, wherein R_2 is alkyl, haloalkyl, alkoxyalkyl or haloalkoxyalkyl and R_{101} , R_{102} , R_{103} , R_{104} are each
independently hydrogen, halogen, or alkyl.

20

9. A compound of claim 7, wherein R_2 is $-CH_2Y$.

10. A compound of claim 9, wherein Y is Q.



11. A compound of claim 2, wherein R_1 is

12. A compound of claim 11, wherein R_2 is alkyl, haloalkyl, alkoxyalkyl or haloalkoxyalkyl and R_{101} , R_{102} , R_{103} , R_{104} are each
5 independently hydrogen, halogen, or alkyl.

13. A compound of claim 11, wherein R_2 is $-\text{CH}_2\text{Y}$.

14. A compound of claim 13, wherein Y is \underline{Q} .

10

15. A compound of claim 1, wherein R_2 is alkoxyalkyl alkyl, haloalkyl or haloalkoxyalkyl

16. A compound of claim 15, wherein R_3 is isoxazol-5-yl or isoxazol-
15 3-yl independently substituted with two substituents selected from alkyl or halogen.

17. A compound of claim 1, wherein R_2 is $-\text{CH}_2\text{Y}$.

18. A compound of claim 17, wherein R_3 is isoxazol-5-yl or isoxazol-
20 3-yl independently substituted with two substituents selected from alkyl or halogen.

19. A compound of claim 17, wherein Y is \underline{Q} .

25

20. A compound of claim 19, wherein R_3 is isoxazol-5-yl or isoxazol-
3-yl independently substituted with two substituents selected from alkyl or halogen.

21. A compound of claim 1, wherein said compound is selected from
 N,4-Diethyl-1-[[2'-[[[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl-2-
 methyl][1,1'-biphenyl]-4-yl]methyl]-2-propyl-1H-imidazole-5-carboxamide;
 5 1-[[2'-[[[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl-2-methyl][1,1'-biphenyl]-4-
 yl]methyl]-4-ethyl-N-(1-methylethyl)-2-propyl-1H-imidazole-5-carboxamide;
 N-(4,5-Dimethyl-3-isoxazolyl)-2'-ethoxymethyl-4'-[[[(6-ethyl-3-methoxy-2-
 methyl-4-pyridinyl)oxy]methyl] [1,1'-biphenyl]-2-sulfonamide;
 4'-[(5-Acetyl-4-ethyl-2-propylimidazol-1-yl)methyl]-N-(4,5-dimethyl-
 10 3-isoxazolyl)-2'-methyl[1,1'-biphenyl]-2-sulfonamide;
 N-(4,5-Dimethyl-3-isoxazolyl)-4'-[[[(6-ethyl-3-methoxy-2-methyl-4-
 pyridinyl)oxy]methyl]-2'-propyl [1,1'-biphenyl]-2-sulfonamide;
 and salts, enantiomers, diastereomers and metabolites thereof.
22. A compound of claim 1, wherein said compound is selected from
 N,4-Diethyl-1-[[2'-[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl-2-
 methyl][1,1'-biphenyl]-4-yl]methyl]-2-propyl-1H-imidazole-5-carboxamide;
 1-[[2'-[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl-2-methyl][1,1'-
 biphenyl]-4-yl]methyl]-4-ethyl-N-(1-methylethyl)-2-propyl-1H-imidazole-5-
 20 carboxamide;
 N-(3,4-Dimethyl-5-isoxazolyl)-2'-ethoxymethyl-4'-[[[(6-ethyl-3-
 methoxy-2-methyl-4-pyridinyl)oxy]methyl] [1,1'-biphenyl]-2-sulfonamide;
 4'-[(5-Acetyl-4-ethyl-2-propylimidazol-1-yl)methyl]-N-(3,4-dimethyl-
 5-isoxazolyl)-2'-methyl[1,1'-biphenyl]-2-sulfonamide;
 25 N-(3,4-Dimethyl-5-isoxazolyl)-4'-[[[(6-ethyl-3-methoxy-2-methyl-4-
 pyridinyl)oxy]methyl]-2'-propyl [1,1'-biphenyl]-2-sulfonamide;
 (S)-2-[N-[2'-[[N-(5-Methyl-3-isoxazolyl)amino]sulfonyl][1,1'-
 biphenyl]-4-yl]methyl]-N-(1-oxopentyl)amino]-3,N-dimethylbutanamide;
 (S)-2-[N-[2'-[[N-(4-Bromo-5-methyl-3-isoxazolyl)amino]sulfonyl][1,1'-
 30 biphenyl]-4-yl]methyl]-N-(1-oxopentyl)amino]-3,N-dimethylbutanamide;
 4'-[(2-Ethylquinolin-4-yl)oxymethyl]-N-(5-methylisoxazol-3-yl)

- [1,1'-biphenyl]-2-sulfonamide;
4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4-bromo-5-methyl-3-isoxazolyl)-2'-[(3,3-dimethyl-2-oxo-1-pyrrolidinyl)methyl][1,1'-biphenyl]-2-sulfonamide;
- 5 N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N-methyl-2-pyrazinecarboxamide;
N-[[2'-[(4,5-Dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl)methyl]-N-(1-oxopentyl)-L-valine;
- 10 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-cyano-N-(4,5-dimethyl-3-isoxazolyl)[1,1'-biphenyl]-2-sulfonamide;
(S)-N-[[2'-[(4,5-Dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl)methyl]-N-(1-piperidinyl)carbonylpropylpentanamide;
and salts, enantiomers, diastereomers and metabolites thereof.
- 15
23. A method for the treatment of an endothelin-dependent or angiotensin II-dependent disorder (such as hypertension, pulmonary hypertension, primary pulmonary hypertension, low renin hypertension, male erectile dysfunction, male or female sexual dysfunction, heart failure, atherosclerosis, restenosis, endotoxemia, inhibition of cell growth, cancer, migraine, asthma, ischemia, subarachnoid hemorrhage, benign
- 20 prostatic hypertrophy, renal glomerular or mesangial cell disorders, acute or chronic renal failure, chronic obstructive pulmonary disease, pain associated with prostate cancer, organ damage associated with the cell proliferative effects of endothelin, general morbidity and mortality
- 25 associated with endothelin-dependent or angiotensin II-dependent disorders, diabetic nephropathy, and dementia), comprising the step of administering to a subject in need thereof an amount effective therefor of at least one compound of claim 1.

24. A pharmaceutical composition for the treatment of an endothelin-dependent or angiotensin II-dependent disorder, comprising a pharmaceutically acceptable vehicle or diluent and at least one compound of claim 1 in an amount effective therefor.

5

25. A compound of claim 1, wherein said compound is selected from the group consisting of:

- N-(4,5-Dimethyl-3-isoxazolyl)-4'-[[6-ethyl-3-methoxy-2-methyl-4-pyridinyl]oxy]methyl]-2'-ethyl [1,1'-biphenyl]-2-sulfonamide;
- 10 N-(3,4-Dimethyl-5-isoxazolyl)-4'-[[6-ethyl-3-methoxy-2-methyl-4-pyridinyl]oxy]methyl]-2'-ethyl [1,1'-biphenyl]-2-sulfonamide;
- N-(4,5-Dimethyl-3-isoxazolyl)-4'-[[3-methoxy-2-methyl-6-propyl-4-pyridinyl]oxy]methyl]-2'-ethyl [1,1'-biphenyl]-2-sulfonamide;
- 15 N-(3,4-Dimethyl-5-isoxazolyl)-4'-[[3-methoxy-2-methyl-6-propyl-4-pyridinyl]oxy]methyl]-2'-ethyl [1,1'-biphenyl]-2-sulfonamide;
- N-(4,5-Dimethyl-3-isoxazolyl)-4'-[[3-methoxy-2-methyl-6-propyl-4-pyridinyl]oxy]methyl]-2'-(ethoxymethyl) [1,1'-biphenyl]-2-sulfonamide;
- N-(3,4-Dimethyl-5-isoxazolyl)-4'-[[3-methoxy-2-methyl-6-propyl-4-pyridinyl]oxy]methyl]-2'-(ethoxymethyl) [1,1'-biphenyl]-2-sulfonamide;
- 20 N-(4,5-Dimethyl-3-isoxazolyl)-4'-[[3-methoxy-2-methyl-6-propyl-4-pyridinyl]oxy]methyl]-2'-propyl [1,1'-biphenyl]-2-sulfonamide;
- N-(3,4-Dimethyl-5-isoxazolyl)-4'-[[3-methoxy-2-methyl-6-propyl-4-pyridinyl]oxy]methyl]-2'-propyl [1,1'-biphenyl]-2-sulfonamide;
- N-(4,5-Dimethyl-3-isoxazolyl)-4'-[[3-ethoxy-6-ethyl-2-methyl-4-pyridinyl]oxy]methyl]-2'-ethyl [1,1'-biphenyl]-2-sulfonamide;
- 25 N-(3,4-Dimethyl-5-isoxazolyl)-4'-[[3-ethoxy-6-ethyl-2-methyl-4-pyridinyl]oxy]methyl]-2'-ethyl [1,1'-biphenyl]-2-sulfonamide;
- N-(4,5-Dimethyl-3-isoxazolyl)-4'-[[3-ethoxy-6-ethyl-2-methyl-4-pyridinyl]oxy]methyl]-2'-ethoxymethyl [1,1'-biphenyl]-2-sulfonamide;
- 30 N-(3,4-Dimethyl-5-isoxazolyl)-4'-[[3-ethoxy-6-ethyl-2-methyl-4-pyridinyl]oxy]methyl]-2'-ethoxymethyl [1,1'-biphenyl]-2-sulfonamide;

N-(4,5-Dimethyl-3-isoxazolyl)-4'-[[[(3-ethoxy-6-ethyl-2-methyl-4-pyridinyl)oxy]methyl]-2'-propyl [1,1'-biphenyl]-2-sulfonamide;

N-(3,4-Dimethyl-5-isoxazolyl)-4'-[[[(3-ethoxy-6-ethyl-2-methyl-4-pyridinyl)oxy]methyl]-2'-propyl [1,1'-biphenyl]-2-sulfonamide;

5 N-(4,5-Dimethyl-3-isoxazolyl)-4'-[[[(3-ethoxy-2-methyl-6-propyl-4-pyridinyl)oxy]methyl]-2'-ethyl [1,1'-biphenyl]-2-sulfonamide;

N-(3,4-Dimethyl-5-isoxazolyl)-4'-[[[(3-ethoxy-2-methyl-6-propyl-4-pyridinyl)oxy]methyl]-2'-ethyl [1,1'-biphenyl]-2-sulfonamide;

10 N-(4,5-Dimethyl-3-isoxazolyl)-4'-[[[(3-ethoxy-2-methyl-6-propyl-4-pyridinyl)oxy]methyl]-2'-ethoxymethyl [1,1'-biphenyl]-2-sulfonamide;

N-(3,4-Dimethyl-5-isoxazolyl)-4'-[[[(3-ethoxy-2-methyl-6-propyl-4-pyridinyl)oxy]methyl]-2'-ethoxymethyl [1,1'-biphenyl]-2-sulfonamide;

N-(4,5-Dimethyl-3-isoxazolyl)-4'-[[[(3-ethoxy-2-methyl-6-propyl-4-pyridinyl)oxy]methyl]-2'-propyl [1,1'-biphenyl]-2-sulfonamide;

15 N-(3,4-Dimethyl-5-isoxazolyl)-4'-[[[(3-ethoxy-2-methyl-6-propyl-4-pyridinyl)oxy]methyl]-2'-propyl [1,1'-biphenyl]-2-sulfonamide;

N-(4,5-Dimethyl-3-isoxazolyl)-4'-[[[(2,6-dimethyl-3-ethoxy-4-pyridinyl)oxy]methyl]-2'-ethyl [1,1'-biphenyl]-2-sulfonamide;

20 N-(3,4-Dimethyl-5-isoxazolyl)-4'-[[[(2,6-dimethyl-3-ethoxy-4-pyridinyl)oxy]methyl]-2'-ethyl [1,1'-biphenyl]-2-sulfonamide;

N-(4,5-Dimethyl-3-isoxazolyl)-4'-[[[(2,6-dimethyl-3-ethoxy-4-pyridinyl)oxy]methyl]-2'-ethoxymethyl [1,1'-biphenyl]-2-sulfonamide;

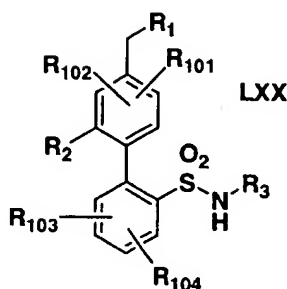
N-(3,4-Dimethyl-5-isoxazolyl)-4'-[[[(2,6-dimethyl-3-ethoxy-4-pyridinyl)oxy]methyl]-2'-ethoxymethyl [1,1'-biphenyl]-2-sulfonamide;

25 N-(4,5-Dimethyl-3-isoxazolyl)-4'-[[[(2,6-dimethyl-3-ethoxy-4-pyridinyl)oxy]methyl]-2'-propyl [1,1'-biphenyl]-2-sulfonamide;

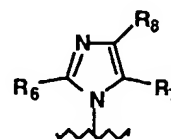
N-(3,4-Dimethyl-5-isoxazolyl)-4'-[[[(2,6-dimethyl-3-ethoxy-4-pyridinyl)oxy]methyl]-2'-propyl [1,1'-biphenyl]-2-sulfonamide;

and salts, enantiomers, diastereomers and metabolites thereof.

26. A compound of formula LXX, or an enantiomer, diastereomer, salt or metabolite thereof



- 5 wherein R_2 , R_{101} , R_{102} , R_{103} , R_{104} are as defined in claim 1;
 R_3 is isoxazol-5-yl or isoxazol-3-yl independently substituted with two
 substituents selected from alkyl or halogen; and
 R_1 is any group such that the resulting compound demonstrates affinity
 (IC_{50}) for both the AT_1 receptor and ET_A receptor of less than 5
 10 micromolar at both receptors.



27. A compound of claim 2, wherein R_1 is M.

28. A compound of claim 27, wherein R_2 is alkyl, haloalkyl,
 alkoxyalkyl or haloalkoxyalkyl and R_{101} , R_{102} , R_{103} , R_{104} are each
 15 independently hydrogen, halogen, or alkyl.

29. A compound of claim 27, wherein R_2 is $-CH_2Y$.

30. A compound of claim 29, wherein Y is Q.

20

31. A crystalline form of 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-2'-(ethoxymethyl) [1,1'-biphenyl]-2-sulfonamide having a melting point of about 148°C.

32. A compound of claim 1 selected from
- 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-3'-chloro-N-(4,5-dimethyl-3-isoxazolyl)-5-methoxy[1,1'-biphenyl]-2-sulfonamide;
- 5 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-3'-fluoro-4-methoxy[1,1'-biphenyl]-2-sulfonamide;
- 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-5'-chloro-N-(4,5-dimethyl-3-isoxazolyl)-2'-fluoro-4-methoxy[1,1'-biphenyl]-2-sulfonamide;
- 10 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-3'-chloro-N-(4,5-dimethyl-3-isoxazolyl)-4-methoxy[1,1'-biphenyl]-2-sulfonamide;
- 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-4-methoxy[1,1'-biphenyl]-2-sulfonamide;
- 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-2'-(ethoxymethyl)-4-methoxy[1,1'-biphenyl]-2-sulfonamide;
- 15 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-3'-fluoro-5-methoxy[1,1'-biphenyl]-2-sulfonamide;
- 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-5'-chloro-N-(4,5-dimethyl-3-isoxazolyl)-2'-fluoro-5-methoxy[1,1'-biphenyl]-2-sulfonamide;
- 20 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-5-methoxy[1,1'-biphenyl]-2-sulfonamide;
- 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-2'-(ethoxymethyl)-5-methoxy[1,1'-biphenyl]-2-sulfonamide;
- 25 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-3'-fluoro-4,5-dimethoxy[1,1'-biphenyl]-2-sulfonamide;

- 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-5'-chloro-N-(4,5-dimethyl-3-isoxazolyl)-2'-fluoro-4,5-dimethoxy[1,1'-biphenyl]-2-sulfonamide;
- 5 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-3'-chloro-N-(4,5-dimethyl-3-isoxazolyl)-4,5-dimethoxy[1,1'-biphenyl]-2-sulfonamide;
- 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-4,5-dimethoxy[1,1'-biphenyl]-2-sulfonamide;
- 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-2'-(ethoxymethyl)-4,5-dimethoxy[1,1'-biphenyl]-2-sulfonamide;
- 10 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-5'-chloro-N-(4,5-dimethyl-3-isoxazolyl)-2'-fluoro[1,1'-biphenyl]-2-sulfonamide;
- 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-3'-chloro-N-(4,5-dimethyl-3-isoxazolyl)[1,1'-biphenyl]-2-sulfonamide;
- 15 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-4-methoxy-3'-methyl[1,1'-biphenyl]-2-sulfonamide;
- 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-3'-fluoro-4-methoxy[1,1'-biphenyl]-2-sulfonamide;
- 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-3'-methyl[1,1'-biphenyl]-2-sulfonamide;
- 20 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-5-fluoro[1,1'-biphenyl]-2-sulfonamide;
- N²-(Cyclopropylcarbonyl)-N²-[[2'-[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl)methyl]-N-methyl-L-
- 25 valinamide;
- N²-[[2'-[(4,5-Dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl)methyl]-N,3-dimethyl-N²-(1-oxobutyl)-L-valinamide;
- N²-[[2'-[(4,5-Dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl)methyl]-N-methyl-N²-(2-methyl-1-oxopropyl)-L-valinamide;

N²-(Cyclopentylcarbonyl)-N²-[[2'-[[[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-methyl-L-valinamide;

5 N²-[[2'-[[[(4,5-Dimethyl-3-isoxazolyl)amino]sulfonyl]-3-fluoro[1,1'-biphenyl]-4-yl]methyl]-N-methyl-N²-(1-oxobutyl)-L-valinamide;

N²-[[2'-[[[(4,5-Dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-(1-methylethyl)-N²-(1-oxobutyl)-L-valinamide;

N²-[[2'-[[[(4,5-Dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-(2-methoxyethyl)-N²-(1-oxobutyl)-L-valinamide;

10 N-(Cyclopropylmethyl)-N²-[[2'-[[[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N²-(1-oxobutyl)-L-valinamide;

N²-[[2'-[[[(4,5-Dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N²-(1-oxobutyl)-N-(3-pyridinyl)-L-valinamide;

15 N²-[[2'-[[[(4,5-Dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-methyl-N²-(1-oxopentyl)-L-valinamide;

N-Methyl-N²-[[2'-[[[(5-methyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N²-(1-oxopentyl)-L-valinamide;

20 N²-[[2'-[[[(4,5-Dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-ethyl-N²-(1-oxobutyl)-L-valinamide;

N²-[[2'-[[[(4,5-Dimethyl-3-isoxazolyl)amino]sulfonyl]-5'-fluoro[1,1'-biphenyl]-4-yl]methyl]-N-methyl-N²-(1-oxobutyl)-L-valinamide;

N-(4,5-Dimethyl-3-isoxazolyl)-4'-[[[(2,6-dimethyl-3-methoxy-4-pyridinyl)oxy]methyl][1,1'-biphenyl]-2-sulfonamide;

25 N-(4,5-Dimethyl-3-isoxazolyl)-4'-[[[(2,6-dimethyl-3-methoxy-4-pyridinyl)oxy]methyl]-3'-fluoro[1,1'-biphenyl]-2-sulfonamide;

N-(4,5-Dimethyl-3-isoxazolyl)-4'-[(1,4,5,6,7,8-hexahydro-8-oxo-2-propyl-1-cycloheptimidazolyl)methyl][1,1'-biphenyl]-2-sulfonamide;

30 N-(4,5-Dimethyl-3-isoxazolyl)-3'-fluoro-4'-[(1,4,5,6,7,8-hexahydro-8-oxo-2-propyl-1-cycloheptimidazolyl)methyl][1,1'-biphenyl]-2-sulfonamide;

N-(4,5-Dimethyl-3-isoxazolyl)-5-fluoro-4'-[(1,4,5,6,7,8-hexahydro-8-oxo-2-propyl-1-cycloheptimidazolyl)methyl][1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-2'-(hydroxymethyl)[1,1'-biphenyl]-2-sulfonamide;

5 N-[[2'-[(4,5-Dimethyl-3-isoxazolyl)amino]sulfonyl]-2-(ethoxymethyl)[1,1'-biphenyl]-4-yl)methyl]-1-[(1-oxopentyl)amino]cyclopentanamide;

and salts, enantiomers, diastereomers and metabolites thereof.

10 33. A compound of claim 1 selected from

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-3'-chloro-N-(3,4-dimethyl-5-isoxazolyl)-5-methoxy[1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-3'-fluoro-4-methoxy[1,1'-biphenyl]-2-sulfonamide;

15 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-5'-chloro-N-(3,4-dimethyl-5-isoxazolyl)-2'-fluoro-4-methoxy[1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-3'-chloro-N-(3,4-dimethyl-5-isoxazolyl)-4-methoxy[1,1'-biphenyl]-2-sulfonamide;

20 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-4-methoxy[1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-(ethoxymethyl)-4-methoxy[1,1'-biphenyl]-2-sulfonamide;

25 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-3'-fluoro-5-methoxy[1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-5'-chloro-N-(3,4-dimethyl-5-isoxazolyl)-2'-fluoro-5-methoxy[1,1'-biphenyl]-2-sulfonamide;

30 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-5-methoxy[1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-(ethoxymethyl)-5-methoxy[1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-3'-fluoro-4,5-dimethoxy[1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-5'-chloro-N-(3,4-dimethyl-5-isoxazolyl)-2'-fluoro-4,5-dimethoxy[1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-3'-chloro-N-(3,4-dimethyl-5-isoxazolyl)-4,5-dimethoxy[1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-4,5-dimethoxy[1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-(ethoxymethyl)-4,5-dimethoxy[1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-5'-chloro-N-(3,4-dimethyl-5-isoxazolyl)-2'-fluoro[1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-3'-chloro-N-(3,4-dimethyl-5-isoxazolyl)[1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-4-methoxy-3'-methyl[1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-3'-fluoro-4-methoxy[1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-3'-methyl[1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-5-fluoro[1,1'-biphenyl]-2-sulfonamide;

N²-(Cyclopropylcarbonyl)-N²-[[2'-[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl)methyl]-N-methyl-L-valinamide;

- N^2 -[[2'-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N,3-dimethyl- N^2 -(1-oxobutyl)-L-valinamide;
- N^2 -[[2'-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-methyl- N^2 -(2-methyl-1-oxopropyl)-L-valinamide;
- 5 N^2 -(Cyclopentylcarbonyl)- N^2 -[[2'-[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-methyl-L-valinamide;
- N^2 -[[2'-[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl]-3-fluoro[1,1'-biphenyl]-4-yl]methyl]-N-methyl- N^2 -(1-oxobutyl)-L-valinamide;
- 10 N^2 -[[2'-[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-(1-methylethyl)- N^2 -(1-oxobutyl)-L-valinamide;
- N^2 -[[2'-[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-(2-methoxyethyl)- N^2 -(1-oxobutyl)-L-valinamide;
- N -(Cyclopropylmethyl)- N^2 -[[2'-[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]- N^2 -(1-oxobutyl)-L-valinamide;
- 15 N^2 -[[2'-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]- N^2 -(1-oxobutyl)-N-(3-pyridinyl)-L-valinamide;
- N^2 -[[2'-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-methyl- N^2 -(1-oxopentyl)-L-valinamide;
- 20 N -Methyl- N^2 -[[2'-[[[(3-methyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]- N^2 -(1-oxopentyl)-L-valinamide;
- N^2 -[[2'-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-ethyl- N^2 -(1-oxobutyl)-L-valinamide;
- 25 N^2 -[[2'-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl]-5'-fluoro[1,1'-biphenyl]-4-yl]methyl]-N-methyl- N^2 -(1-oxobutyl)-L-valinamide;
- N -(3,4-Dimethyl-5-isoxazolyl)-4'-[[[(2,6-dimethyl-3-methoxy-4-pyridinyl)oxy]methyl][1,1'-biphenyl]-2-sulfonamide;
- N -(3,4-Dimethyl-5-isoxazolyl)-4'-[[[(2,6-dimethyl-3-methoxy-4-pyridinyl)oxy]methyl]-3'-fluoro[1,1'-biphenyl]-2-sulfonamide;
- 30

N-(3,4-Dimethyl-5-isoxazolyl)-4'-[(1,4,5,6,7,8-hexahydro-8-oxo-2-propyl-1-cycloheptimidazolyl)methyl][1,1'-biphenyl]-2-sulfonamide;

N-(3,4-Dimethyl-5-isoxazolyl)-3'-fluoro-4'-[(1,4,5,6,7,8-hexahydro-8-oxo-2-propyl-1-cycloheptimidazolyl)methyl][1,1'-biphenyl]-2-sulfonamide;

5 N-(3,4-Dimethyl-5-isoxazolyl)-5-fluoro-4'-[(1,4,5,6,7,8-hexahydro-8-oxo-2-propyl-1-cycloheptimidazolyl)methyl][1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-(hydroxymethyl)[1,1'-biphenyl]-2-sulfonamide;

10 N-[[2'-[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl]-2-(ethoxymethyl)[1,1'-biphenyl]-4-yl)methyl]-1-[(1-oxopentyl)amino]cyclopentanamide;

and salts, enantiomers, diastereomers and metabolites thereof.

34. The compound 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-2'-(2-fluoroethoxymethyl) [1,1'-biphenyl]-2-sulfonamide or a salt, enantiomer, diastereomer or metabolite thereof.

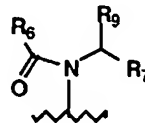
35. The compound 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-2'-propyl [1,1'-biphenyl]-2-sulfonamide or a salt, enantiomer, diastereomer or metabolite thereof.

36. The compound N-(4,5-Dimethyl-3-isoxazolyl)-2'-ethoxymethyl-4'-[[[(3-methoxy-2,6-dimethyl-4-pyridinyl)oxy]methyl] [1,1'-biphenyl]-2-sulfonamide or a salt, enantiomer, diastereomer or metabolite thereof.

37. The compound N-(4,5-Dimethyl-3-isoxazolyl)-2'-[(2-fluoroethoxy)methyl]-4'-[[[(3-methoxy-2,6-dimethyl-4-pyridinyl)oxy]methyl] [1,1'-biphenyl]-2-sulfonamide or a salt, enantiomer, diastereomer or metabolite thereof.

30

38. The compound N-(4,5-Dimethyl-3-isoxazolyl)-4'-[[[(3-methoxy-2,6-dimethyl-4-pyridinyl)oxy]methyl]-2'-propyl [1,1'-biphenyl]-2-sulfonamide or a salt, enantiomer, diastereomer or metabolite thereof.



5 39. A compound of claim 2, where in R_1 is D.

40. A compound of claim 39, wherein R_2 is hydrogen, alkyl, haloalkyl, alkoxyalkyl or haloalkoxyalkyl and R_{101} , R_{102} , R_{103} , R_{104} are each independently hydrogen, halogen, or alkyl.

10

41. A compound of claim 39 wherein R_2 is $-CH_2Y$.

42. A compound of claim 41, wherein Y is Q.

15

43. A compound of claim 1 wherein R_3 is other than pyridyl when R_1 is A.

20 44. The pharmaceutical composition of claim 46 further comprising at least one ACE inhibitor (such as captopril, zofenopril, fosinopril, ceranapril, alacepril, enalapril, delapril, pentopril, quinapril, ramipril, or lisinopril), vasopepsidase inhibitor (such as omapatrilat or gemopatrilat), HMG CoA reductase inhibitor (such as pravastatin, lovastatin, atorvastatin, simvastatin, NK-104 or ZD-
25 4522), anti-platelet agent (such as clopidigrel, ticlopidine, CS-747 or aspirin), anti-diabetic agent (such as biguanides or biguanide/glyburide combinations), beta-adrenergic agent (such as

carvedilol or metoprolol), or mineralocorticoid receptor antagonist (such as spironolactone or eplerenone).

45. The compound (+)-4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-
5 en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-2'-(ethoxymethyl) [1,1'-
biphenyl]-2-sulfonamide or metabolites and salts thereof.

46. The compound (-)-4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-
en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-2'-(ethoxymethyl) [1,1'-
10 biphenyl]-2-sulfonamide or metabolites and salts thereof.